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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,308	08/21/2003	Paul B. J. Burton	3432-US-NP	9578

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EXAMINER	
JIANG, DONG	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,308	BURTON ET AL.	
	Examiner	Art Unit	
	DONG JIANG	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-49,51,52 and 64-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-49,51,52 and 64-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 13 November 2009 is acknowledged and entered. Following the amendment, claims 31-45, 50, 53, 55-63 are canceled, and claims 46, 51 and 64 are amended.

Currently, claims 46-49, 51, 52 and 64-67 are pending and under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 50 and 63 are moot as the applicant has canceled the claim.

The scope of enablement rejection of claims 46-49, 51, 52 and 64-67 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment.

The lack of written description rejection of claims 46-49 and 52 under 35 U.S.C. 112, first paragraph is withdrawn in view of applicant's amendment.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46-49, 51 and 52 remain rejected, and claims 64-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waelti (US2004/0028687) and Yudestad et al. (Cardiovasc Res., 2002 Apr; 54(1):175-82, provided by applicants), and in view of Goodwin et al. (US5,674,704, provided by applicants), for the reasons of record set forth in the previous Office Action mailed on 5/13/09.

Applicants argument filed on 13 November 2009 has been fully considered, but is not deemed persuasive for the reasons below.

At pages 5-6 of the response, applicants maintain the previous argument that Yndestad actually teaches away from selection of 4-1BB as the target to antagonize, since upregulation of 4-1BBL in peripheral blood mononuclear cells could not be confirmed using RT-PCR, and receptors for 4-BBL were not known to be expressed in the heart (page 180 of Yndestad et al.); and that none of the patients screened in Yndestad et al. suffered from chronic heart failure induced by treatment with chemotherapeutic agents such as doxorubicin. This argument is not persuasive because upregulation of 4-1BBL not being confirmed in a particular experiment (RT-PCR) is, by no means, "teaching away" from selection of 4-1BB as the target to antagonize. In fact, Yndestad states "[N]otably, for both 4-1BBL and CD40L the hybridisation signals were low. Obviously, the quantification of low abundance transcripts will be vulnerable to variations in background levels and sensitivity, in contrast to the more abundant transcripts", indicating the technical difficulty in the detection. Further, contrary to applicants argument, Yndestad clearly teaches that 4-1BB ligand (L), and other members of the TNF superfamily were upregulated in CHF (abstract; page 178, Table 3; and page 179, 1st column, 2nd paragraph; for example). Further, CHF is a condition, which can be the result of many causes. Therefore, regardless of the causes, the end result (CHF) is the same.

At page 6 of the response, Applicants question the use of the reference to Waelti to allegedly show that doxorubicin can result in cardiotoxicity often resulting in cardiomyopathy with serious congestive heart failure, as US application 2004/0028687 to Waelti was *published* 2/12/04, after the filing date of the provisional applications to which the instant application claims priority (the instant application claims priority to provisional applications 60/406,418 filed 8/28/02, and 60/494,457 filed 8/12/03), therefore, Waelti was not publicly available to one

of ordinary skill in the art at the time of the invention. This argument is not persuasive because Waelti (US2004/0028687), filed on 1/15/03, claims priority to provisional applications 60/349,609 filed on 1/15/02, which predates the earliest effective filing date (8/28/02) of the present application. It is the *effective filing date* of the Waelti, which is relied upon for the instant rejection since the prior art reference is an *US patent application* (102(e) date). Applicants further argue that Waelti does not describe the basic inventive concept of the instantly pending claims (Waelti describes synthetic membrane vesicles for delivery of therapeutic substances), and was only relied on for a few sentences in paragraph [0022], which amounts to background information in that reference, therefore, the reference to Waelti as a whole does not teach or suggest the claimed subject matter. This argument is not persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co*., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, on page 6 of the response, Applicants maintain the previous argument that the Examiner has not provided any motivation to combine these references in the manner done by the Examiner, and these references have no apparent relationship to each other, and Waelti et al. was not even published at the time of the invention; and that the combination of references was only selected in hindsight as provided by the instant application, which is not a proper basis for an obviousness rejection. This argument is not persuasive because, as addressed previously, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Waelti teaches that one of the greatest limitations of cancer chemotherapy agents such as are the severe side effects accompanying the use of some of the most broadly active antitumor agents, such as doxorubicin, which can cause dose-dependent cardiotoxicity often resulting in irreversible cardiomyopathy with serious congestive heart failure; Yudestad teaches that besides TNFα as a pathogenic factor in CHF, other members of the TNF superfamily including 4-1BB-L may potentially be even more important; and Goodwin teaches

soluble 4-1BB polypeptides, which retain the ability to bind the 4-1BB ligand, and fusion proteins thereof suitable for therapeutic applications. Therefore, the combined teachings of the prior art references made it obvious to use Goodwin's soluble 4-1BB fusion protein for the treatment of cardiomyopathy/ CHF including those caused by anthracycline compounds such as doxorubicin (taught by Waelti), targeting 4-1BB-L, which is a member of the TNF superfamily, and is overexpressed in CHF patients (by Yudestad). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

With respect to claims 64-67, Goodwin teaches the isolation of the Human 4-1BB (Example 2, columns 19-20), which amino acid sequence of SEQ ID NO:8 is 100% identical to the present SEQ ID NO:18. Additionally, Goodwin teaches that the soluble form (the extracellular domain) of the human 4-1BB protein comprises amino acids 1-163 of SEQ ID NO:8 (column 5, lines 4-5). Further, Goodwin teaches that the soluble 4-1BB polypeptides retain the ability to bind the 4-1BB ligand (column 4, lines 21-30), and are advantageous for certain therapeutic purposes (column 4, lines 53-56). Furthermore, Goodwin teaches oligomeric (multimeric) forms of the inventive proteins including dimeric and trimeric forms of the 4-1BB proteins, which may exhibit enhanced biological activity compared to the monomeric forms (column 5, lines 48-56), and as an example, a fusion protein comprises two or three soluble 4-1BB-L or 4-1BB polypeptides linked via a peptide linker (column 6, lines 57-59).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to use Goodwin's soluble form of the 4-1BB comprising amino acids 1-163 of SEQ ID NO:8, or an oligomer thereof for the treatment of cardiomyopathy/CHF including those caused by anthracycline compounds such as doxorubicin (taught by Waelti), as Yudestad teaches that 4-1BB-L, a member of the TNF superfamily, is overexpressed in CHF patients; while TNFα is a pathogenic factor in CHF, other members of the TNF superfamily may potentially be even more important; and that the enhanced expression of ligands in the TNF

superfamily may reflect a potential pathogenic role of these cytokines in CHF. The person of ordinary skill in the art would have been motivated to do so for treating cardiomyopathy/CHF, and reasonably would have expected success because Goodwin has teaches that the soluble 4-1BB retains the ability to bind the 4-1BB ligand, therefore, it would prohibit the binding of the 4-1BB ligand to its receptor, and is a 4-1BB antagonist

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dong Jiang/
Primary Examiner, Art Unit 1646
2/6/10